Elie Hatem, Nadine El Banna, Meng-Er Huang (2017 May 24)

**Multifaceted roles of glutathione and glutathione-based systems in carcinogenesis and anticancer drug resistance.**


**Summary**

Glutathione is the most abundant antioxidant molecule in living organisms and has multiple functions. Intracellular glutathione homeostasis, through its synthesis, consumption, and degradation is an intricately balanced process. Glutathione levels are often high in tumor cells prior to treatment and there is a strong correlation between elevated levels of intracellular glutathione/sustained glutathione-mediated redox activity and resistance to pro-oxidant anticancer therapy. Recent Advances: Ample evidence demonstrates that glutathione and glutathione-based systems are particularly relevant in cancer initiation, progression, and the development of anticancer drug resistance.

Anh Thu Bui, Meng-Er Huang, Maryline Havard, Fanny Laurent-Tchenio, François Dautry, Thierry Tchenio (2017 May 3)

**Transient exposure to androgens induces a remarkable self-sustained quiescent state in dispersed prostate cancer cells.**

*Cell cycle (Georgetown, Tex.)*: 879-893 : [DOI: 10.1080/15384101.2017.1310345](https://doi.org/10.1080/15384101.2017.1310345)

**Summary**

Cellular quiescence is a reversible cell growth arrest that is often assumed to require a persistence of non-permissive external growth conditions for its maintenance. In this work, we showed that androgen could induce a quiescent state that is self-sustained in a cell-autonomous manner through a “hit and run” mechanism in androgen receptor-expressing prostate cancer cells. This phenomenon required the set-up of a sustained redox imbalance and TGFβ/BMP signaling that were dependent on culturing cells at low density. At medium cell density, androgens failed to induce such a self-sustained quiescent state, which correlated with a lesser induction of cell redox imbalance and oxidative stress markers like CDKN1A. These effects of androgens could be mimicked by transient overexpression of CDKN1A that triggered its own expression and a sustained SMAD phosphorylation in cells cultured at low cell density. Overall, our data suggest that self-sustained but fully reversible quiescent states might constitute a general response of dispersed cancer cells to stress conditions.

Meng-Er Huang, Céline Facca, Zakaria Fatmi, Dorothée Baïlle, Safia Bénakli, Laurence Vernis (2016)

**Summary**

Cellular quiescence is a reversible cell growth arrest that is often assumed to require a persistence of non-permissive external growth conditions for its maintenance. In this work, we showed that androgen could induce a quiescent state that is self-sustained in a cell-autonomous manner through a “hit and run” mechanism in androgen receptor-expressing prostate cancer cells. This phenomenon required the set-up of a sustained redox imbalance and TGFβ/BMP signaling that were dependent on culturing cells at low density. At medium cell density, androgens failed to induce such a self-sustained quiescent state, which correlated with a lesser induction of cell redox imbalance and oxidative stress markers like CDKN1A. These effects of androgens could be mimicked by transient overexpression of CDKN1A that triggered its own expression and a sustained SMAD phosphorylation in cells cultured at low cell density. Overall, our data suggest that self-sustained but fully reversible quiescent states might constitute a general response of dispersed cancer cells to stress conditions.
DNA replication inhibitor hydroxyurea alters Fe-S centers by producing reactive oxygen species in vivo.

*Scientific reports* : 29361 : [DOI: 10.1038/srep29361]

**Summary**

Redox homeostasis is tightly controlled in cells as it is critical for most cellular functions. Iron-Sulfur centers (Fe-S) are metallic cofactors with electronic properties that are associated with proteins and allow fine redox tuning. Following the observation that altered Fe-S biosynthesis is correlated with a high sensitivity to hydroxyurea (HU), a potent DNA replication blocking agent, we identified that oxidative stress response pathway under the control of the main regulator Yap1 attenuates HU deleterious effects, as it significantly increases resistance to HU, Fe-S biosynthesis and DNA replication kinetics in the presence of HU. Yap1 effect is mediated at least in part through up-regulation of two highly conserved genes controlling cytosolic Fe-S biosynthesis and oxidative stress, Dre2 and Tah18. We next observed that HU produces deleterious effects on cytosolic Fe-S clusters in proteins in vivo but not in vitro, suggesting that HU’s impact on Fe-S in vivo is mediated by cellular metabolism. Finally, we evidenced that HU exposure was accompanied by production of reactive oxygen species intracellularly. Altogether, this study provides mechanistic insight on the initial observation that mutants with altered Fe-S biosynthesis are highly sensitive to HU and uncovers a novel mechanism of action of this widely used DNA replication inhibitor.

Year of publication 2015

Tiantian He, Elie Hatem, Laurence Vernis, Ming Lei, Meng-Er Huang (2015 Dec 21)

PRX1 knockdown potentiates vitamin K3 toxicity in cancer cells: a potential new therapeutic perspective for an old drug.


**Summary**

Many promising anticancer molecules are abandoned during the course from bench to bedside due to lack of clear-cut efficiency and/or severe side effects. Vitamin K3 (vitK3) is a synthetic naphthoquinone exhibiting significant in vitro and in vivo anticancer activity against multiple human cancers, and has therapeutic potential when combined with other anticancer molecules. The major mechanism for the anticancer activity of vitK3 is the generation of cytotoxic reactive oxygen species (ROS). We thus reasoned that a rational redox modulation of cancer cells could enhance vitK3 anticancer efficiency.